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Article

Prenatal Exposure to Ambient Pesticides and Adverse Birth Outcomes in Agricultural Regions of California

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Abstract: Findings from studies of prenatal exposure to pesticides and adverse birth outcomes have been equivocal so far. We examined prenatal exposure to agricultural pesticides in relation to preterm birth and term low birthweight, respectively, in children born between 1998 and 2010 randomly selected from California birth records. We estimated residential exposures to agriculturally applied pesticides within 2 km of residential addresses at birth by pregnancy trimester for 17 individual pesticides and 3 chemical classes (organophosphates, pyrethroids, and carbamates). Among maternal addresses located within 2 km of any agricultural pesticide application, we identified 24,693 preterm and 220,297 term births, and 4,412 term low birthweight and 194,732 term normal birthweight infants. First or second trimester exposures to individual pesticides (e.g., glyphosates, paraquat, imidacloprid) or exposures to 2+ pesticides in the three chemical classes were associated with small increases (3-7%) in risk for preterm birth; associations were stronger for female offspring. We did not find associations between term low birthweight and exposures to pesticides other than for myclobutanil (OR: 1.11; 95% CI: 1.04-1.20) and possibly pyrethroids as a class. Our improved exposure assessment revealed that first and second trimester exposures to pesticides were associated with preterm delivery but few affected term low birthweight.

Keywords: Agricultural pesticides; Residential proximity; Adverse birth outcomes; Preterm birth; Low birthweight; Pregnancy

1. Introduction

During the first decade of the 21st century, the rates of *preterm birth* and *low birthweight* were 11%-13% and 7%-8% in the US, respectively [1]. While survival of infants born preterm and/or low birthweight has improved, these children are at higher risk for adverse health outcomes such as neurodevelopmental

impairment, respiratory and gastrointestinal complications [2,3], obesity, diabetes mellitus, hypertension, and kidney disease [4–6], and infant and childhood mortality [7].

California is the largest agricultural state in the United States, with more than 150 million pesticide active ingredients applied every year [8]. Pesticides have been found in indoor dust at residences near agricultural fields, and may persist for years [9]. Experimental studies show that various pesticides, including organophosphates and pyrethroids, can influence prenatal development including disturbance of placental function [10], endocrine disruption [11], immune regulation and inflammation [12,13].

However, epidemiologic studies examining the effect of pesticides on preterm birth and low birthweight have yielded inconsistent results. While ecological and cross-sectional studies reported positive associations for preterm birth and low birthweight and pesticide use in agriculture [14–16], results from studies assessing self-reported or occupational use of pesticides were inconsistent [17–19]. Nevertheless, small biomarker-based studies with measured organochlorines and/or organophosphates and their metabolic breakdown products in maternal blood, urine, or umbilical cord blood suggested positive associations with preterm birth or with lower birthweight, with variation by chemicals and outcomes assessed [20–22]. A systematic review of 25 studies of residential proximity to pesticide applications suggested weak or no effects on preterm birth and low birthweight, possibly due to misclassification in exposure assessment [23]. Yet more recent residential proximity studies using simple or area-level exposure assessments provided some evidence for pesticides influencing birth outcomes [16,24,25]. Three Geographic Information System (GIS)-based studies of the San Joaquin Valley of California (~1997-2011) reported conflicting results. After summing over all chemicals with acute toxicity based on the US EPA Signal Word [26], one study found pesticide exposures to increase the risk of preterm birth and low birthweight among those exposed to the highest 5th percentile applied within a 2.6 km^2 section [27]. The other two studies assessed ever/never exposure to individual agrochemicals and chemical groups including endocrine disruptors and reproductive toxicants applied within 500 m of residences in relation to spontaneous preterm birth [28] or preeclampsia phenotypes resulting in preterm delivery [29] for exposures in any month of gestation and - contrary to the first study- reported overwhelmingly inverse associations. The discrepancies in results may be explained by various pesticides these studies included, different methods of pesticide exposure assessment, or the exposure period in relation to gestational age they chose.

Our objective was to examine whether prenatal exposure to agricultural pesticides contributes to risk of preterm birth or term low birth weight. We estimated GIS-derived exposures to agricultural pesticides applied near maternal residences during pregnancy selected based on previous research that indicated reproductive toxicity, and considered trimester-specific exposure windows, in all agricultural regions of California (defined as areas with any agricultural pesticide application within 2 km of individuals' residences).

2. Materials and Methods

Study Population

We combined two sets of birth records randomly selected from all California births born between 1998 and 2010; these were: 1) controls matched to children with autism at a 1:10 ratio by sex and birth year (n=339,210) as described previously [30] and, 2) controls matched to children diagnosed with cancers at a 1:20 ratio by birth year (n=143,595) [31], which were representative of all California births. We excluded children with missing data for gestational length based on the date of last reported menses (n=20,124), with extreme or implausible gestational ages (<20 weeks or >45 weeks) or birthweights (<500 g or >6,800 g) (n=6,390), with missing sex (n=2), with home addresses outside of California (n=1,433), and multiple births (n=13,251) and also removed duplicate subjects. The remaining births included 41,089 preterm births, defined as gestational age less than 37 weeks, and 358,256 term births (not low birthweight) that were born

between 37 - <42 weeks as the reference. To examine term low birthweight, we used 7,407 term births with less than 2,500 g birthweight, indicating intrauterine growth restriction and included 317,710 term normal birthweight infants (2,500 g - 4,000 g) in the comparison group. Restricting our study population to those residing at birth within 2 km of fields on which agricultural use pesticides were applied, we included 24,693 preterm births and 220,297 term births, and 4,412 term low birthweight and 194,732 term normal birthweight infants.

Exposure Assessment

We geocoded maternal residential addresses listed on the birth certificates using an automated approach [32] and calculated measures of residential ambient pesticide exposures using a GIS-based Residential Ambient Pesticide Estimation System, as previously described [33,34]. In brief, we combined California's Pesticide Use Reports (PUR), land use maps, and geocoded birth addresses to produce estimates of pesticide exposure during each month of pregnancy (see Supplementary Materials and Methods in Appendix A). Monthly exposure estimates (pounds per acre) were calculated by adding the poundage of pesticide applied in a 2 km buffer surrounding each address and weighting the total poundage by the proportion of acreage treated within the buffer. We defined the first, second, and third trimesters as 0-12 weeks, 13-25 weeks, and ≥26 weeks of pregnancy, respectively. For preterm birth, the length of gestation and hence exposure period are shorter than term birth by design; to account for that, we assessed third trimester exposures using 27-32 weeks of gestation only (>88% of preterm births had a gestational length longer than 32 weeks). For each pesticide, monthly values were divided into daily poundage for each gestational day of pregnancy, which was then averaged across all days in each trimester. Due to the uncertainty in this type of exposure assessment (e.g. assuming the mothers stayed at the reported residences during the entire pregnancy, wind patterns), we categorized prenatal exposure as ever/never exposed to a specific chemical in each trimester.

We selected 17 individual chemicals previously observed to have reproductive toxicity [24,35–39]. Additionally, we also considered all pesticides from three widely used chemical classes in the Pesticide Action Network (PAN) pesticide database (http://www.pesticideinfo.org/) that have been linked to reproductive toxicity [21,37,40,41] , i.e. 24 n-methyl carbamate/dithiocarbamates, 50 organophosphates, and 29 pyrethroid pesticides to which one or more study subjects were exposed according to our 2 km buffer criterion (Table S1). For each class, we used the count of individual chemicals that each subject was ever exposed to in each trimester. We divided subjects into exposed to 2+ pesticides, exposed to 1 pesticide, and no exposure to the respective pesticides.

Since specific location of non-agricultural pesticide applications (structural pest control, rights of way, and landscape maintenance in urban communities) are not provided by the PUR, and due to competing exposures such as air pollution in urban areas [42,43], we restricted our analyses to individuals born in agricultural regions, defined as residences within a 2 km buffer of any type of agricultural pesticide application during pregnancy (Figure S1).

Statistical Analysis

We conducted unconditional logistic regression analyses adjusting for matching factors (infant sex and year of birth) and the source of control subjects (autism vs cancer study) to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between pesticide exposures and preterm birth or term low birthweight. To account for the unbalanced sex ratio (~4:1 male: female among the autism controls) and birth year distribution in this combined sample, we included the inverse of the sampling fraction (calculated as the sample size divided by total births in California by gender and birth year) as a stabilized weighting factor to reflect the sex and birth year distribution of all California births. We additionally adjusted for potential confounders based on the literature [44–47], including: maternal age at delivery (≤19, 20-24, 25-29, 30-34, ≥35), maternal race/ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific islander, others), maternal birthplace (US vs. non-US), maternal education (<12 years, 12 years, 13-15 years, ≥16 years), parity (1, 2, ≥3), payment source for prenatal care as a proxy for family income

(private/HMO/Blue Cross Blue Shield vs. MediCal/government/self-pay), prenatal care in the first trimester (yes vs. no), and neighborhood-level socioeconomic status (SES) [48]. Furthermore, we conducted stratified analyses by maternal race/ethnicity (non-Hispanic Whites, US-born Hispanics, and non-US-born Hispanics) since exposures may be higher among Hispanics, especially recent immigrants, who may live close to agricultural fields and have poor housing conditions [49]; by infant sex because males are more likely to be born preterm [50,51]; as well as by season of conception (Jan-Mar, Apr-Jun, Jul-Sep, and Oct-Dec), estimated from the last menstrual period and length of gestation, because of seasonal variations in pesticide applications (Figure 1). We also conducted several sensitivity analyses to evaluate the robustness of our findings, including adjusting for additional confounders such as maternal cigarette smoking, pre-pregnancy Body Mass Index (BMI), or air pollution, adjusting for co-exposures to other pesticides in the same exposure window or exposures during earlier windows, or restricting our analyses to births with a high geocode quality or with spontaneous vaginal deliveries (see Appendix A). Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Infants born preterm or born term with low birthweight were more likely to have mothers of younger age, less education, lower neighborhood SES, starting prenatal care after the first trimester, who used Medi-Cal or other government programs instead of private insurance. In addition, preterm births were more likely to be a third or later born child, and have mothers with Hispanic or Black race/ethnic origin; term low birthweight infants were more likely to be female and a first born child, and born to Black and Asian mothers (Table 1).

Exposure to some pesticides in the first- and second trimester was associated with a small increase in risk for preterm birth (ORs: 1.03~1.07) (Table 2) while third trimester exposures did not increase risk for preterm birth. Effect estimates were slightly stronger in female infants, except for simazine, which showed stronger effects in males with ORs of 1.06~1.07 (Table S2). Stratified analysis by season of conception suggested that effect estimates were generally stronger when the peak season of pesticide application concurred with the first or second trimester of pregnancy (data not shown).

When examining chemical classes, first trimester exposures to carbamates ($OR_{1st\ trimester}$: 1.04; 95% CI: 1.00-1.08), or pyrethroids ($OR_{1st\ trimester}$: 1.06; 95% CI: 1.02-1.09) increased ORs for preterm birth in the group exposed to 2+ chemicals compared with no exposure (Table 3), while second trimester exposures to carbamates, organophosphates, or pyrethroids were all associated with small increases (3-6%) in ORs for preterm birth. In sex specific analyses, we did not observe elevated ORs for preterm birth among male infants, but observed slightly stronger increases (7–11%) with exposure during the first or second trimester among female infants (Table 4). Exposure prevalence was highest in infants born to non-US-born Hispanic mothers, followed by US-born Hispanic mothers, and in general pesticide ORs were stronger in these two groups; however, we did not observe a single racial/ethnic subgroup with stronger effect estimates across all three chemical classes (Table S3).

Associations between the selected individual pesticides or chemical classes and term low birthweight for each trimester in pregnancy were mostly null. In multivariable adjusted models, we only estimated increased ORs for second or third-trimester exposures to myclobutanil ($OR_{2nd\ trimester}$: 1.11; 95% CI: 1.03-1.19; $OR_{3rd\ trimester}$: 1.11; 95% CI: 1.04-1.20 (Table S4); similarly, exposures to the three chemical classes were not associated with term low birthweight in general, except for marginally elevated odds ($OR_{1st\ trimester}$: 1.05; 95% CI: 0.98, 1.13; $OR_{2nd\ trimester}$: 1.06; 95% CI: 0.99, 1.13) in infants exposed to 2 or more pyrethroids (Table S5).

Figures and Tables

180 Table 1. Demographic and pregnancy characteristics of the study population in agricultural regions, 1998-
181 2010.

	Preterm Birth		Term Birth		Term Low Birthweight		Term Normal Birthweight	
	N=24,693	%	N=220,297	%	N=4,412	%	N=194,732	%
Infant sex								
Males	18,586	75.3	161,076	73.1	2,972	67.4	140,308	72.1
Females	6,107	24.7	59,221	26.9	1,440	32.6	54,424	27.9
Year of Birth								
1998	1,393	5.6	12,327	5.6	262	5.9	10,728	5.5
1999	1,483	6.0	12,599	5.7	228	5.2	10,944	5.6
2000	1,504	6.1	14,190	6.4	293	6.6	12,381	6.4
2001	1,661	6.7	14,759	6.7	279	6.3	12,856	6.6
2002	1,808	7.3	15,882	7.2	319	7.2	13,846	7.1
2003	2,043	8.3	17,993	8.2	365	8.3	15,684	8.1
2004	2,127	8.6	18,030	8.2	385	8.7	15,924	8.2
2005	2,127	8.6	18,860	8.6	361	8.2	16,824	8.6
2006	2,200	8.9	19,797	9.0	409	9.3	17,680	9.1
2007	2,440	9.9	20,616	9.4	448	10.2	18,412	9.5
2008	2,359	9.6	21,950	10.0	445	10.1	19,696	10.1
2009	2,063	8.4	19,155	8.7	349	7.9	17,160	8.8
2010	1,485	6.0	14,139	6.4	269	6.1	12,597	6.5
Maternal Age								
19 or less	2,976	12.1	21,126	9.6	593	13.4	19,711	10.1
20-24	5,772	23.4	50,362	22.9	1,045	23.7	45,392	23.3
25-29	5,922	24.0	59,782	27.1	1,139	25.8	52,667	27.0
30-34	5,590	22.6	53,719	24.4	938	21.3	46,661	24.0
35 and older	4,432	17.9	35,306	16.0	696	15.8	30,299	15.6
Missing	1	0.0	2	0.0	1	0.0	2	0.0
Maternal Education								
<12 years	8,238	33.4	62,459	28.4	1,351	30.6	55,856	28.7
12 years	6,955	28.2	58,683	26.6	1,249	28.3	51,883	26.6
13-15 years	4,949	20.0	45,809	20.8	866	19.6	40,122	20.6
16+ years	3,984	16.1	48,252	21.9	827	18.7	42,367	21.8
Missing	567	2.3	5,094	2.3	119	2.7	4,504	2.3
Maternal Race/Ethnicity								

White, non-Hispanic	5,919	24.0	64,600	29.3	928	21.0	55,036	28.3
Hispanic, any race	13,801	55.9	116,509	52.9	2,278	51.6	103,428	53.1
Black	1,691	6.8	9,639	4.4	392	8.9	8,843	4.5
Asian/PI	2,437	9.9	21,570	9.8	587	13.3	20,193	10.4
Other/Refused	845	3.4	7,979	3.6	227	5.1	7,232	3.7
Parity								
1	9,319	37.7	84,535	38.4	2,238	50.7	76,877	39.5
2	7,060	28.6	70,977	32.2	1,087	24.6	62,329	32.0
3 or more	8,306	33.6	64,736	29.4	1,084	24.6	55,484	28.5
Missing	8	0.0	49	0.0	3	0.1	42	0.0
Prenatal care in first trimester								
Yes	19821	80.3	186741	84.8	3533	80.1	164640	84.5
No	4580	18.5	32233	14.6	834	18.9	28891	14.8
Missing	292	1.2	1323	0.6	45	1.0	1201	0.6
Payment type of prenatal care								
Private/HMO/BCBS	10731	43.5	110816	50.3	1961	44.4	96650	49.6
MediCal/Govt/self-pay	13591	55.0	108385	49.2	2401	54.4	97085	49.9
Missing	371	1.5	1096	0.5	50	1.1	997	0.5
Maternal birthplace								
US	13585	55.0	119055	54.0	2337	53.0	104048	53.4
Non-US countries	11093	44.9	101169	45.9	2072	47.0	90618	46.5
Missing	15	0.1	73	0.0	3	0.1	66	0.0
Quintiles of neighborhood SES								
1 (Lowest)	7157	29.0	55746	25.3	1254	28.4	49635	25.5
2	6403	25.9	55227	25.1	1174	26.6	48916	25.1
3	5143	20.8	45378	20.6	883	20.0	39879	20.5
4	3451	14.0	35467	16.1	627	14.2	31215	16.0
5 (Highest)	2525	10.2	28364	12.9	474	10.7	24980	12.8
Missing	14	0.1	115	0.1	.	.	107	0.1

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Table 2. Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never) and preterm birth.

	First trimester				Second trimester			
Pesticide	Preterm Birth*	Term Birth*	OR[1]	OR[2]	Preterm Birth*	Term Birth*	OR[1]	OR[2]
Fungicide								
Myclobutanil	5307 (22.0%)	47755 (21.6%)	1.02 (0.99, 1.05)	1.02 (0.99, 1.06)	5366 (22.2%)	48337 (21.9%)	1.02 (0.98, 1.05)	1.02 (0.99, 1.06)
Chlorothalonil	5511 (22.8%)	49183 (22.3%)	1.03 (1.00, 1.06)	1.02 (0.99, 1.05)	5585 (23.1%)	49070 (22.2%)	1.05 (1.02, 1.08)	1.04 (1.01, 1.08)
Mancozeb	3600 (14.9%)	32779 (14.8%)	1.00 (0.96, 1.04)	0.98 (0.95, 1.02)	3588 (14.8%)	33038 (15.0%)	0.99 (0.95, 1.02)	0.97 (0.94, 1.01)
Herbicide								
Glyphosate compounds	14346 (59.3%)	127703 (57.8%)	1.07 (1.04, 1.10)	1.05 (1.02, 1.08)	14295 (59.1%)	127672 (57.8%)	1.06 (1.03, 1.09)	1.04 (1.01, 1.07)
Paraquat dichloride	3850 (15.9%)	32073 (14.5%)	1.11 (1.07, 1.16)	1.07 (1.03, 1.11)	3823 (15.8%)	32009 (14.5%)	1.11 (1.07, 1.15)	1.06 (1.02, 1.10)
Simazine	2613 (10.8%)	23310 (10.6%)	1.02 (0.98, 1.07)	1.02 (0.97, 1.06)	2684 (11.1%)	22978 (10.4%)	1.07 (1.03, 1.12)	1.06 (1.02, 1.11)
Insecticide								
Chlorpyrifos	8511 (35.2%)	74414 (33.7%)	1.06 (1.04, 1.10)	1.03 (1.00, 1.06)	8390 (34.7%)	74037 (33.5%)	1.05 (1.02, 1.08)	1.02 (0.99, 1.05)
Abamectin	7715 (31.9%)	68819 (31.2%)	1.04 (1.01, 1.07)	1.02 (0.99, 1.05)	7736 (32.0%)	69606 (31.5%)	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)
Malathion	5696 (23.6%)	51530 (23.3%)	1.01 (0.98, 1.04)	0.99 (0.96, 1.03)	5715 (23.6%)	51429 (23.3%)	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)
Imidacloprid	6107	53105	1.07	1.06	6139	54444	1.04	1.04

	(25.3%)	(24.0%)	(1.04, 1.10)	(1.03, 1.10)	(25.4%)	(24.6%)	(1.01, 1.08)	(1.00, 1.07)
Diazinon	5319	46514	1.05	1.02	5185	45430	1.05	1.02
	(22.0%)	(21.1%)	(1.01, 1.08)	(0.99, 1.06)	(21.4%)	(20.6%)	(1.01, 1.08)	(0.99, 1.06)
Permethrin	4597	40300	1.05	1.03	4465	40533	1.01	0.99
	(19.0%)	(18.2%)	(1.02, 1.09)	(1.00, 1.07)	(18.5%)	(18.3%)	(0.97, 1.04)	(0.95, 1.02)
Dimethoate	3223	27905	1.06	1.04	3216	27874	1.06	1.03
	(13.3%)	(12.6%)	(1.02, 1.10)	(1.00, 1.08)	(13.3%)	(12.6%)	(1.02, 1.10)	(0.99, 1.07)
Methyl bromide	2448	21398	1.04	1.05	2337	20851	1.02	1.01
	(10.1%)	(9.7%)	(1.00, 1.09)	(1.00, 1.10)	(9.7%)	(9.4%)	(0.98, 1.07)	(0.96, 1.06)
Carbaryl	2241	20285	1.00	1.00	2150	20160	0.97	0.96
	(9.3%)	(9.2%)	(0.96, 1.05)	(0.96, 1.05)	(8.9%)	(9.1%)	(0.92, 1.01)	(0.92, 1.01)
Phosmet	1154	9995	1.05	1.01	1099	9875	1.01	0.97
	(4.8%)	(4.5%)	(0.99, 1.12)	(0.95, 1.08)	(4.5%)	(4.5%)	(0.95, 1.08)	(0.91, 1.04)
Methyl parathion	448	3660	1.11	1.05	402	3715	0.98	0.91
	(1.9%)	(1.7%)	(1.01, 1.23)	(0.95, 1.17)	(1.7%)	(1.7%)	(0.88, 1.08)	(0.82, 1.01)

[1] Adjusted for year of birth, infant sex

[2] Adjusted for year of birth, infant sex, maternal age, maternal education, maternal race/ethnicity, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

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Table 3. Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth.

	First trimester					Second trimester				
Chemical Class	Preterm Birth*	Term Birth*	OR[1]	OR[2]	OR[3]	Preterm Birth*	Term Birth*	OR[1]	OR[2]	OR[3]
No. of carbamates ever exposed to										
0 (ref.)	15419 (63.8%)	143956 (65.2%)				15343 (63.5%)	143806 (65.1%)			
1	4519 (18.7%)	40328 (18.3%)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)	1.01 (0.98, 1.05)	4604 (19.0%)	40390 (18.3%)	1.07 (1.03, 1.10)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)
2+	4237 (17.5%)	36613 (16.6%)	1.08 (1.04, 1.11)	1.04 (1.00, 1.08)	1.01 (0.97, 1.06)	4227 (17.5%)	36702 (16.6%)	1.07 (1.04, 1.11)	1.04 (1.00, 1.08)	1.03 (0.98, 1.08)
No. of organophosphates ever exposed to										
0 (ref.)	9523 (39.4%)	90246 (40.9%)				9469 (39.2%)	90715 (41.1%)			
1	5105 (21.1%)	46306 (21.0%)	1.04 (1.01, 1.08)	1.01 (0.98, 1.05)	1.00 (0.96, 1.04)	5263 (21.8%)	46494 (21.0%)	1.08 (1.04, 1.12)	1.06 (1.02, 1.10)	1.04 (1.00, 1.08)
2+	9546 (39.5%)	84346 (38.2%)	1.07 (1.03, 1.10)	1.02 (0.99, 1.06)	0.98 (0.94, 1.02)	9442 (39.1%)	83688 (37.9%)	1.07 (1.04, 1.11)	1.03 (1.00, 1.06)	0.99 (0.95, 1.03)
No. of pyrethroids ever exposed to										
0 (ref.)	11938 (49.4%)	112936 (51.1%)				11906 (49.3%)	112617 (51.0%)			
1	4965	44681	1.05	1.03	1.03	4977	44247	1.06	1.04	1.03

	(20.5%)	(20.2%)	(1.01, 1.09)	(0.99, 1.06)	(0.99, 1.07)	(20.6%)	(20.0%)	(1.02, 1.10)	(1.00, 1.08)	(0.99, 1.07)
	7272	63281	1.09	1.06	1.06	7291	64034	1.08	1.05	1.04
2+	(30.1%)	(28.6%)	(1.05, 1.12)	(1.02, 1.09)	(1.01, 1.11)	(30.2%)	(29.0%)	(1.04, 1.11)	(1.01, 1.08)	(0.99, 1.08)

[1] Adjusted for year of birth, infant sex

[2] Adjusted for year of birth, infant sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

[3] Adjusted for year of birth, infant sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, neighborhood SES, and co-exposures to other two chemical classes

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Table 4. Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth, stratified by infant sex.

	First trimester				Second trimester			
Chemical Class	Preterm Birth*	Term Birth*	OR[1]	OR[2]	Preterm Birth*	Term Birth*	OR[1]	OR[2]
	Males							
No. of carbamates ever exposed to								
0 (ref.)	11978 (64.4%)	104716 (64.9%)			11937 (64.2%)	104618 (64.8%)		
1	3408 (18.3%)	29803 (18.5%)	1.00 (0.96, 1.04)	0.99 (0.95, 1.03)	3466 (18.6%)	29761 (18.4%)	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)
2+	3215 (17.3%)	26835 (16.6%)	1.05 (1.00, 1.09)	1.01 (0.97, 1.06)	3198 (17.2%)	26974 (16.7%)	1.04 (1.00, 1.08)	1.00 (0.96, 1.05)
No. of organophosphates ever exposed to								
0 (ref.)	7352 (39.5%)	65519 (40.6%)			7320 (39.4%)	65953 (40.9%)		
1	3973 (21.4%)	33934 (21.0%)	1.04 (1.00, 1.09)	1.02 (0.97, 1.06)	4055 (21.8%)	34148 (21.2%)	1.07 (1.03, 1.11)	1.05 (1.01, 1.09)
2+	7276 (39.1%)	61901 (38.4%)	1.05 (1.01, 1.08)	1.01 (0.97, 1.04)	7226 (38.8%)	61253 (38.0%)	1.06 (1.02, 1.10)	1.02 (0.98, 1.06)
No. of pyrethroids ever exposed to								
0 (ref.)	9239 (49.7%)	82215 (51.0%)			9281 (49.9%)	82055 (50.9%)		
1	3902 (21.0%)	32699 (20.3%)	1.06 (1.02, 1.10)	1.03 (0.99, 1.08)	3822 (20.5%)	32618 (20.2%)	1.03 (0.99, 1.08)	1.01 (0.97, 1.06)
2+	5460 (29.4%)	46440 (28.8%)	1.04 (1.01, 1.08)	1.01 (0.98, 1.05)	5498 (29.6%)	46681 (28.9%)	1.04 (1.00, 1.08)	1.01 (0.97, 1.05)
	Females							
No. of carbamates ever exposed to								
0 (ref.)	3861 (63.1%)	38769 (65.5%)			3835 (62.6%)	38723 (65.4%)		
1	1171 (19.1%)	10682 (18.0%)	1.09 (1.02, 1.17)	1.08 (1.00, 1.15)	1195 (19.5%)	10731 (18.1%)	1.12 (1.05, 1.20)	1.09 (1.01, 1.17)
2+	1090 (17.8%)	9783 (16.5%)	1.11 (1.03, 1.19)	1.07 (1.00, 1.15)	1091 (17.8%)	9778 (16.5%)	1.12 (1.04, 1.20)	1.08 (1.01, 1.17)

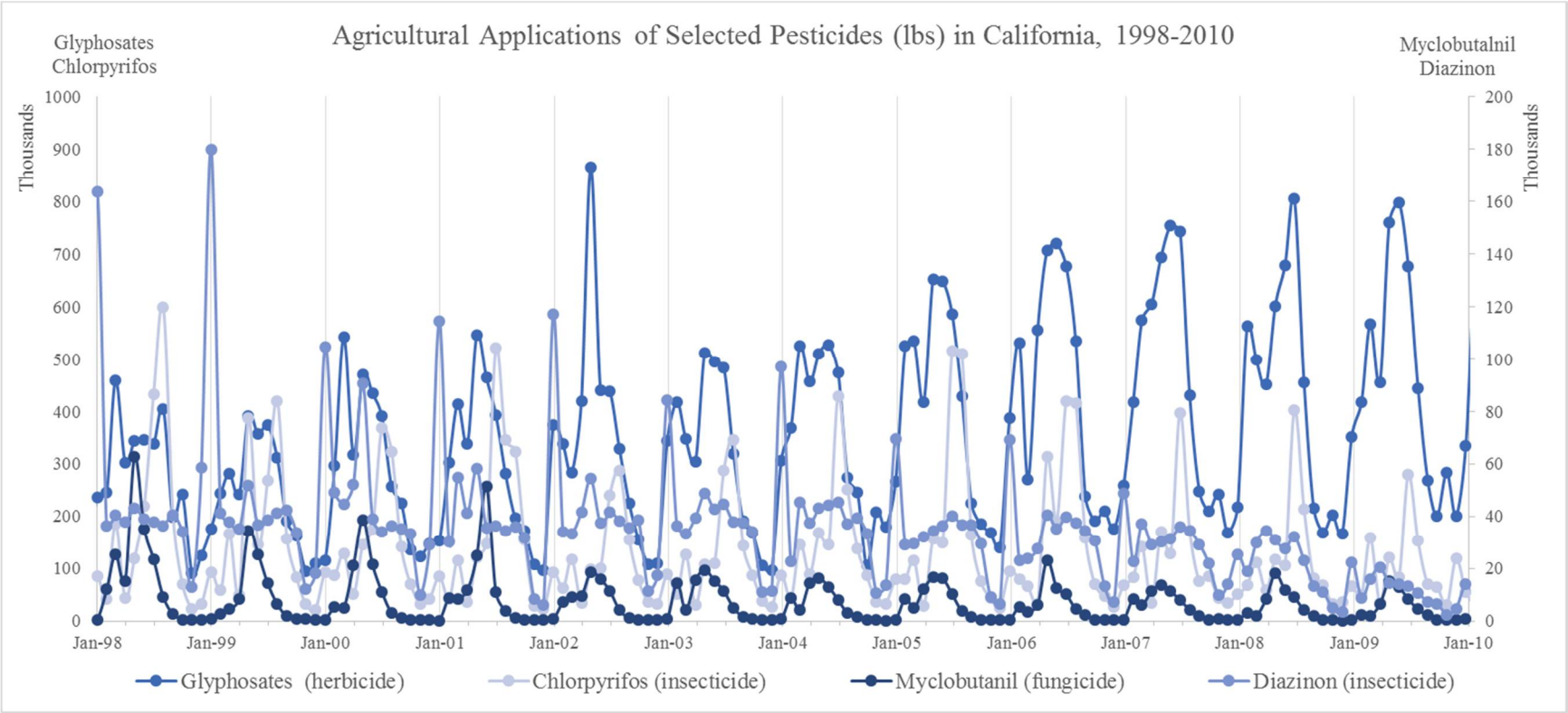
No. of organophosphates ever exposed to								
0 (ref.)	2402 (39.2%)	24352 (41.1%)			2385 (39.0%)	24443 (41.3%)		
1	1276 (20.8%)	12375 (20.9%)	1.04 (0.97, 1.12)	1.01 (0.94, 1.09)	1331 (21.7%)	12396 (20.9%)	1.10 (1.02, 1.18)	1.07 (1.00, 1.15)
2+	2444 (39.9%)	22506 (38.0%)	1.09 (1.03, 1.16)	1.04 (0.98, 1.11)	2406 (39.3%)	22394 (37.8%)	1.09 (1.03, 1.16)	1.04 (0.98, 1.11)
No. of pyrethroids ever exposed to								
0 (ref.)	3003 (49.0%)	30390 (51.3%)			2969 (48.5%)	30277 (51.1%)		
1	1226 (20.0%)	11958 (20.2%)	1.04 (0.97, 1.11)	1.02 (0.95, 1.09)	1263 (20.6%)	11751 (19.8%)	1.09 (1.02, 1.17)	1.08 (1.00, 1.16)
2+	1893 (30.9%)	16886 (28.5%)	1.14 (1.07, 1.21)	1.11 (1.04, 1.18)	1889 (30.9%)	17206 (29.0%)	1.12 (1.05, 1.19)	1.09 (1.02, 1.16)

[1] Adjusted for year of birth

[2] Adjusted for year of birth, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Figure 1. Seasonal variation of selected pesticide applications.



4. Discussion

In this large California study, we compared birth outcomes among women living within 2 km of any type of agricultural pesticide applications during pregnancy. We found that first- and second trimester exposure to selected individual pesticides known or suspected to be reproductive toxicants were associated with a small to moderate size increase in risk of preterm birth. Early and mid-pregnancy exposure to chemicals in the classes of pyrethroids, which have come into use in more recent years, and possibly carbamates and organophosphates, were also linked to preterm birth. We found few pesticides if any to be associated with term low birthweight, except pyrethroids as a class, and myclobutanil - possibly a chance observation given that we examined 17 individual chemicals. Yet, term low birthweight is rarer than preterm birth, thus we have less statistical power to estimate small effect sizes accurately.

The positive associations with preterm birth are consistent with earlier small biomarker-based studies [21,52]. This is in contrast with much of the epidemiologic literature to date that presented little evidence for associations of ambient pesticide exposure with preterm birth thus far [23]. Less than a handful of studies conducted in the US examined associations for environmental exposures to pesticides from agricultural applications and preterm birth and/or low birthweight and also provided month- or trimester-specific estimates [24,27–29]. These studies were almost exclusively conducted using California's PUR system; nevertheless, they differed from each other and our study in terms of study region, exposure assessment methods, specific pesticides, and outcome assessment. Our California-wide study restricting to those living near actively farmed fields is most comparable with an earlier study that focused on residents of the San Joaquin Valley and assessed pesticides labeled with EPA signal word toxicity by summing up their active ingredients applied in a 2.6 km^2 section surrounding maternal residences; this study reported that exposure to all pesticides in the top 5^{th} percentile in pounds applied increased risk of preterm birth and low birthweight by 5-9% overall [27]. However, this method is problematic because 1) the use of total poundage of all pesticides fails to distinguish between high volume but less toxic agents, and low volume but highly toxic agents, and 2) even if the pesticides were assessed according to their known acute toxicity, this may not reflect reproductive toxicity. Therefore, the potential for exposure misclassification and insufficient exploration of the contributions of individual pesticides or pesticide classes with reproductive toxicity limits the results. In contrast to the abovementioned findings, two other studies restricted their sample to all residents of the San Joaquin Valley instead, which included some major cities/towns, and reported overwhelmingly negative associations between 543 specific chemicals and 69 chemical classes (any vs no), even for reproductive toxicants and endocrine disruptors, and spontaneous preterm deliveries [28] or preeclampsia with preterm deliveries [29] in 1998-2011 births. However, these two studies focused mainly on exposures during the month prior to delivery rather than early or mid-pregnancy, which are critical exposure periods for placenta development and preterm birth [53,54]. Our sensitivity analysis stratified by season of conception is in line with this as we found increased risk for exposures in early and not late pregnancy. It is quite possible that results for late pregnancy exposures are affected by a 'live-birth selection bias' [55], i.e. that the most susceptible fetuses exposed to pesticides were lost in early pregnancy. The live-birth bias may lead to underestimation of a possible true effect of exposure in early pregnancy and could even create a spurious protective association in late pregnancy such that only those who were less susceptible to the exposure survived to late pregnancy and these groups may in general have a lower risk for these birth outcomes. Moreover, due to seasonality of pesticide applications, those classified as no or low exposure in late pregnancy could have been highly exposed in early pregnancy during the critical period; thus when estimating effects of late exposure alone, they may seem protective.

Our study suggests that pesticide exposures affect preterm birth mostly in female children, similar to a Chinese study that found high levels of metabolites of organophosphate pesticides in maternal urine to be associated with duration of gestation only in girls [21]. It has been suggested that exposure to pesticides in early pregnancy triggers more spontaneous abortions of male fetuses

[56], or stillbirth in late pregnancy [57], outcomes not captured in our study. It is well known that the male fetus is more vulnerable in utero and is at greater risk of fetal demise with the male-to-female ratio falling from around 120 male conceptions to 105 boys per 100 girls at birth [58]. Some pesticides are endocrine disruptors such as those in the organophosphate family that mimic sex steroidal action and resemble estrogenic more than androgenic action in fish models [59].

Maternal, placental, and fetal factors are thought to determine risk of preterm birth and may be affected by prenatal exposure to environmental chemicals [60–63]. For example, it is known that chlorpyrifos can cross the placenta, possibly affecting fetal growth and development [64]. Mechanisms by which pesticides may affect risks of preterm birth include interference with immune pathways and inflammation [65], or with metabolic and endocrine regulatory pathways [60,62] and oxidative stress [61]. For example, *in-vitro* study results suggested that phosmet and chlorpyrifos alter cell viability and induce an inflammatory cytokine profile, indicating that organophosphates may adversely affect trophoblast cells [39].

In general, we observed stronger associations for births among Hispanic mothers likely because their exposure was higher. According to a recent agricultural survey, about 90% of female farm workers in California were Mexican-born Hispanics [66]; thus, the non-US-born Hispanic mothers may live near fields where they work, making them more likely to be exposed to ambient pesticides when at home. Unfortunately, information on occupations and occupational addresses of the mothers was not available on birth certificates and therefore we could not determine workplace exposures.

Fetal growth restriction, the main reason for low birthweight other than preterm birth, can result from transplacental oxygen and nutrient transport, hypoxia, oxidative stress, placental inflammation, and inhibition of placental growth hormone [67]; these mechanisms may be influenced by toxic exposure to organophosphate and carbamate pesticides [68]. Though we did not find much evidence for associations between term low birthweight and many specific pesticide exposures, others however, reported associations for low birthweight (including preterm low weight births) or a decrease in birthweight for some pesticides, including chlorpyrifos and/or diazinon, carbaryl, methyl bromide, as well as with organophosphate and pyrethroid metabolites measured in maternal urine [18,24,36,41,69]. However, it also has been reported that when adjusting for gestational age, associations with low birthweight were attenuated [69]. Our term low birthweight results may have been underpowered but our findings are in line with previous reports that found exposure to methyl bromide or pyrethroids related to reduced birthweight [24,41].

Most previous pesticide and birth outcome studies examining exposures from home/garden or professional use of pesticides relied on parental interviews after birth [19,70]. These studies have been criticized for their potential selection or recall bias, because mothers who had infants with adverse outcomes may be more likely to participate or recall their pesticide exposures. Other studies using job exposure matrices may have been prone to non-differential exposure measurement errors, and often could not distinguish between types of chemicals. Smaller studies were able to employ biomarkers such as maternal blood or urine collected in pregnancy, or umbilical cord blood samples to measure prenatal chemical concentrations (mostly persistent organochlorines and non-persistent organophosphate metabolites) [20–22]. The necessarily small size of such pregnancy cohorts limits the number of outcomes and hence study power considerably, and they also have to assume that chemical concentrations measured in bio-samples reflect exposures during multiple gestational windows accurately when many pesticides have relatively short half-lives, e.g., hours to a few days for organophosphates [71]. Few studies have multiple bio-samples available throughout pregnancy.

The GIS-PUR and record linkage studies [27–29] including our own do not suffer from selection bias due to non-response or exposure recall bias that threatens interview based studies. However, there are many factors that may affect exposure assessment in these studies including the exposure buffer size, accuracy of birth addresses for assessing pregnancy period exposures, and assumptions about maternal time activity such as time spend at home during days when pesticides are applied. Our GIS approach [34] assesses exposures at a smaller geographic area than PUR data alone (because we incorporate land use data to identify the precise location of crops that PUR data reference), and we consider all linkages between residential locations and sources of pesticide reports (that is, if a pesticide use is mentioned but there is no data on land use for related crops, we include the exposure

based on PUR data alone). This approach is more comprehensive than others reported to date, and is demonstrably more sensitive than using PUR alone [33]. Women living close to fields may be quite different in terms of other exposures and SES from those living in towns or cities in these study areas. Different from previous California studies, we expanded the study area to California statewide but only included mothers living within 2 km of agricultural pesticide applications thus restricting to active farming locations and making unmeasured influences of neighborhood SES or water, soil or air pollution more similar. Other unmeasured sources of pesticide exposure include occupational, home and garden use, or dietary exposures to pesticides which may also be more similar in the women we selected as suggested elsewhere [72].

Our study has some limitations. We assumed that birth addresses reflected the location of mothers over the entirety of pregnancy. A review on residential mobility during pregnancy showed that on average 24% (range 14%-32%) of mothers move during pregnancy in the US [73]. While most moving distances were short (median <10 km), this may still result in exposure misclassification when using a 2 km exposure buffer. Particularly, Hispanic mothers are more mobile than White mothers [73], increasing the chance of exposure misclassification. In addition, data on the potential confounders maternal smoking and pre-pregnancy BMI, were only available for 4 out of 13 study years. However, adjustment for these variables did not change our results more than minimally.

In summary, this study found that first and second but not third trimester exposures to almost all pre-selected pesticides known or suspected to be reproductive toxicants were associated with preterm delivery but only one pesticide (myclobutanil) and perhaps pyrethroids as a class were related to term low birthweight. These associations were stronger in female infants suggesting possible sex specificity for some of these agents or increased vulnerability in male fetuses that would result in selective pregnancy loss.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1,
Table S1: Individual pesticides included in chemical classes;
Table S2: Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never exposed) and preterm birth, stratified by infant sex;
Table S3: Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth, stratified by maternal race/ethnicity;
Table S4: Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never) and term low birthweight;
Table S5: Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and term low birthweight;
Table S6: Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and spontaneous preterm birth;
Figure S1: Study subjects in agricultural and non-agricultural regions.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Supplementary Materials and Methods

Exposure Assessment

In brief, since 1974 agricultural pesticide applications for commercial use are recorded in Pesticide Use Reports (PUR) mandated by the California Department of Pesticide Regulation (CDPR). Each PUR record includes the name of the pesticide's active ingredient, the poundage applied, the crop type, and the location and date of application. The California Department of Water Resources

(CDWR) performs countywide, large-scale surveys of land use and crop cover every 7–10 years. Land use maps increase spatial resolution because they provide more detailed land use geography that allows us to refine the pesticide applications [1]. Previous pesticide studies used different buffer sizes from 500 m [2–5], half a mile (804.5 m) [6], 1000 m [7], 1250 m [8], 1600 m [9], 5000 m [10], to up to 8000 m distances [11], depending on the pesticide of interest, landscape, and weather conditions. Thus, the buffer of 2000 m we chose, will provide a reasonable distance for assessing pesticide applications around residential addresses.

Sensitivity Analyses

In sensitivity analyses, we compared effect estimates with and without adjustment for two risk factors of adverse birth outcomes, maternal cigarette smoking during pregnancy (yes vs. no) and pre-pregnancy Body Mass Index (BMI), calculated as maternal pre-pregnancy weight divided by maternal height (kg/m2) [12,13] for births in 2007-2010 only, since these variables are only available on birth certificates from 2007 onward. We also investigated the potential confounding effects of outdoor air pollution that can impact fetal growth during critical periods [14–16] among the autism controls only due to data availability. We estimated trimester-specific exposures to local, traffic-derived NOx, $PM_{2.5}$, and CO, including roadways within 1.5 km of subjects' birth addresses [17,18], i.e. inter-quartile range (IQR)-scaled measure of NOx as a local traffic marker derived from the CAlifornia LINE source dispersion model (CALINE4) model [19,20]. Additionally, we adjusted for co-exposure to at least one of the other individual chemicals as a single variable (yes/no) when assessing each individual chemical, and estimated mutually adjusted ORs for the three chemical class exposures during the same exposure window. When evaluating later trimester exposures we adjusted for exposure during prior pregnancy periods, because these effect estimates may be altered by earlier exposures [21]. Since birth addresses with a low geocode quality (i.e., at the USPS Zip Code Area centroid level or coarser) due to missing or non-geocodeable fields on the birth certificates (about 12% of all addresses) is likely to introduce spatial exposure misclassification, we excluded those with a geocode quality at the USPS Zip Code Area centroid level or coarser. Lastly, we examined spontaneous vaginal deliveries only, excluding medically indicated preterm deliveries (about 35% of all preterm deliveries in our study population) more likely to be due to severe maternal pregnancy complications including pre-eclampsia [22] and gestational diabetes [23,24] and their etiology might differ from spontaneous preterm deliveries.

Supplementary Results

In our sensitivity analyses, results were similar with additional adjustment for maternal pre-pregnancy BMI and maternal smoking in the years 2007-2010, for NOx as a marker for traffic-related air pollution, or restricting to those with high geocoding quality only. For each individual pesticide, adjusting for co-exposure to other pesticides resulted in attenuation of odds by 2-3%; ORs mutually adjusted for three chemical classes or adjusted for exposures in prior trimesters were mostly unchanged or slightly smaller; the mutually adjusted OR for pyrethroids was most stable, suggesting a more robust association with pyrethroids (Table 3). ORs were slightly stronger when we restricted to spontaneous preterm births only particularly for pyrethroids as a class (Table S6), but were generally similar for individual chemicals or other chemical classes.

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